Catalytic Enantioselective Total Synthesis of (–)-Pyridovericin

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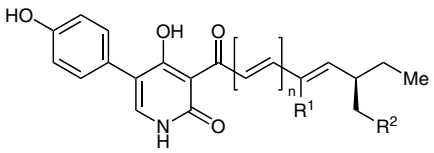
Abstract: The first enantioselective catalytic total synthesis of (–)-pyridovericin is reported. The key steps involve a modified HWE reaction under aqueous conditions and an asymmetric iridium-catalyzed hydrogenation. This resulted in a highly modular and stereoselective approach that delivered the target natural product in high yield and stereoselectivity.

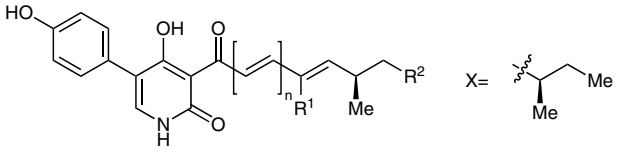
Key words: pyridovericin, total synthesis, natural products, hydrogenation, asymmetric catalysis

Introduction

Entomopathogenic fungi and their extracts, containing pyridone alkaloids, show a wide range of biological activity[2] and they have even found commercial applications, for example as a food supplement in the form of dried *Ophiocordyceps sinensis*, or as microbial pest control agents in the case of *Beauveria bassiana*.[3] Evaluation of these fungal extracts led to the isolation and identification of several pyridone polyene natural products, such as pyridovericin (**1**), torrubiellone C (**2**), militarinone D (**3**), and farinosone A (**4**) (Figure 1); the latter three have recently been synthesized in our laboratories.[4]



n = 1, R^1 = Me, R^2 = OH: pyridovericin (**1**)
n = 2, R^1 = H, R^2 = OH: torrubiellone C (**2**)



n = 2, R^1 = Me, R^2 = X: militarinone D (**3**)
n = 3, R^1 = Me, R^2 = Me: farinosone A (**4**)

Figure 1 Pyridone alkaloid natural products

These compounds all feature a central 4-hydroxy-2-pyridone ring decorated with a 3-acylpolyene side chain and a 5-(4-hydroxyphenyl) substituent. In addition to these structural features, pyridovericin (**1**)[5] and torrubiellone C (**2**)[2a] have a hydroxymethylene substituent in their side chain. Several methodologies, relying on chiral auxiliaries, chiral starting materials, or enzymatic reactions, have been reported for the synthesis of this (hydroxymethyl)ethyl stereogenic center.[6] We have addressed this challenge in the synthesis of torrubiellone C (**2**) by developing a protocol for the asymmetric hydrogenation of silyl-protected 2-(hydroxymethyl)acrylates, culminating in the enantioselective synthesis of torrubiellone C (**2**).[7]

Intrigued by the recently published findings on the potential use of pyridovericin (**1**) as an antiallergenic lead structure,[8] we wanted to apply our asymmetric hydrogenation strategy towards the total synthesis of this compound. Two research groups have previously reported their efforts towards this goal: Baldwin and co-workers published a route to racemic material[10] and a conceptually new quasiracemic approach was reported by Curran and co-workers.[6c] However, the latter approach was plagued by racemization along the synthetic route, and final material with only 15–25% ee, depending on the analysis method, was obtained.[6c] We envisaged avoiding a decrease in the enantiopurity of the intermediates and final products by an iridium-catalyzed asymmetric hydrogenation approach, the results of which are reported here.

Results and Discussion

The synthesis started with the enantioselective hydrogenation of the known silyl-protected β-hydroxy ester **5**[7] using 1 mol% of the iridium catalyst[9] (Scheme 1).

We have previously reported[7] that this hydrogenation can result in enantiomeric purity of up to 95:5 er, but we were not able to consistently reproduce these results. With a new batch of catalyst, we were only able to achieve 94:6 er in screening conditions (80 μmol of substrate), which decreased to 92:8 er on a 0.5-mmol substrate scale. The ligand was determined to be optically pure (>99:1 er) by HPLC on chiral phases, and also the configuration of olefin was determined to be >99% *E* by GC-MS. The workup of the final catalyst–ligand complexation reaction can be delicate, and we therefore suspect that the catalyst itself might contain impurities, although we were not able to observe any by our standard analytical methods.

Nevertheless, the obtained (*S*)-configured ester **6** (99%, 92:8 er) was reduced with diisopropylaluminum hydride to give the aldehyde in 82% yield. Since the aldehyde was

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Biographical Sketches

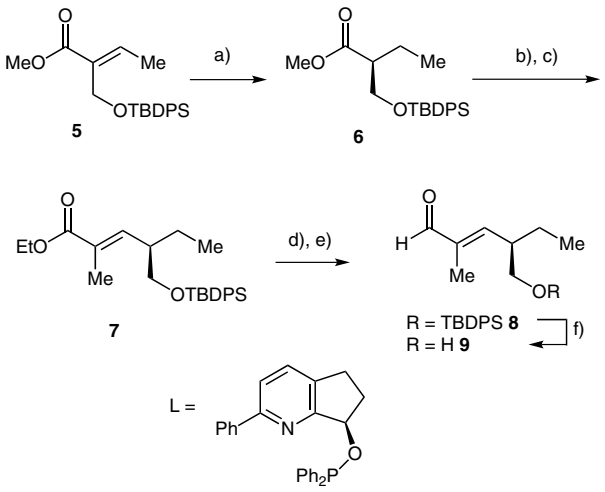
Fabian Schmid (1988) was born and raised in Basel, where he obtained his B.Sc. degree in 2009. He then started his master thesis on the neuritogenic properties of truncated pyridone natural products in the group of Prof. Karl Gademann, graduating in 2011. He continued this work on pyridone alkaloids during his Ph.D. studies, culminating in the total synthesis of (–)-pyridovericin, and is now involved in a new total synthesis project.

Maurizio Bernasconi was born in 1985 in Mendrisio, Switzerland. He obtained his B.Sc. and M.Sc. degrees in chemistry from the ETH Zürich, during the latter carrying out a research project at the University of California, Berkeley under the supervision of Prof. F. D. Toste. In 2009 he moved to Basel (Switzerland) for an internship in the medicinal chemistry laboratories of Hoffmann-La Roche before joining the laboratory of Prof. Andreas Pfaltz at the University of Basel, where he is conducting his doctoral studies focused on the iridium-catalyzed asymmetric hydrogenation of new substrate classes.

Henning Jacob Jessen (1978) obtained his Ph.D. from the University of Hamburg, Germany, working on pronucleotides in the group of Prof. Chris Meier. From 2008–2011 he worked as a postdoctoral fellow (DFG Stipend) in the group of Prof. Karl Gademann at the EPFL and University of Basel, Switzerland. In this research project he developed synthetic approaches towards pyridone alkaloids and studied these natural products in phenotypic assays. In 2011 he moved to the University of Zürich, Switzerland, beginning his habilitation (Liebig Stipend, SNF Ambizione Fellow) in the group of Prof. Jay Siegel and Prof. John Robinson. His current research is focused on the chemical biology of densely phosphorylated natural products.

Andreas Pfaltz (born 1948) obtained a Ph.D. degree from ETH Zürich under the direction of Albert Eschenmoser in 1978. After postdoctoral research with Gilbert Stork at Columbia University he returned to ETH for his Habilitation. From 1990–1995 he was Professor of Organic Chemistry at the University of Basel and from 1995–1998 director at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. In 1999, he returned to the University of Basel to his current position as Professor of Chemistry. His research focuses on catalytic methods for organic synthesis, with special emphasis on asymmetric catalysis. His contributions have been recognized with a number of awards, including the Prelog Medal from ETH, the Noyori Prize, and the Yamada–Koga Prize.

Karl Gademann (born 1972) was educated at ETH Zürich and Harvard University (Ph.D. with Prof. Dr. Dieter Seebach, postdoctoral studies with Prof. Dr. Eric N. Jacobsen, Habilitation associated with Prof. Dr. Erick M. Carreira). His first faculty appointment was at the EPFL Lausanne, and since 2010, he has been professor at the University of Basel. He has had over ninety publications, holds two patents, and received several awards including the Novartis Early Career Award, the National Latsis Prize, Lilly Lecture Award, the Ruzicka Medal, and the Liebig Lectureship of the GDCh. He was awarded the European Young Investigator grant related to natural product synthesis research. His research interests include the synthesis and chemical biology of natural products.



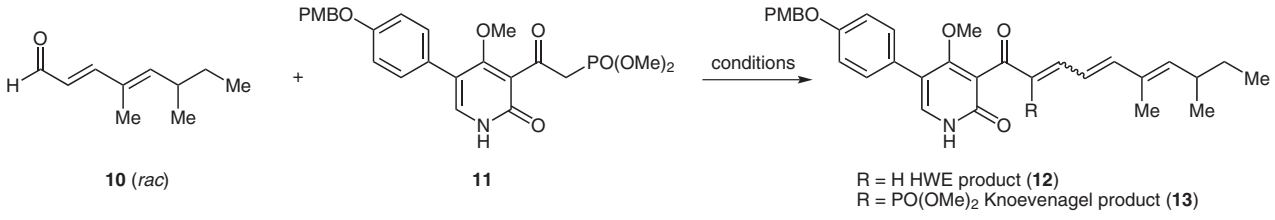
Scheme 1 *Reagents and conditions*: (a) [Ir(L)(cod)]{B[3,5-$(CF_3)_2C_6H_3]_4$} (1 mol%), H_2 (50 bar), CH_2Cl_2, 0 °C, 16 h, 99%, 92:8 er; (b) DIBAL-H (1.15 equiv), CH_2Cl_2, –78 °C, 1 h, 82%; (c) ethyl 2-(triphenylphosphoranylidene)propanoate (2.0 equiv), CH_2Cl_2, reflux, 48 h, 95%; *E*/*Z* >30:1; (d) DIBAL-H (3.0 equiv), THF, –78 °C to r.t., 2 h, 88%; (e) TPAP (2.5 mol%), NMO (1.5 equiv), CH_2Cl_2, r.t., 1 h, 99%; (f) TBAF (1.0 equiv), THF, r.t., 2 h, 95%.

prone to decomposition, it was immediately olefinated in a Wittig reaction[11] and the unsaturated ester **7** was obtained (95%, 91:9 er) with complete *E*-selectivity. A reduction–oxidation sequence (DIBAL-H; TPAP, NMO,[12] 87% over 2 steps) gave the protected α,β-unsaturated aldehyde **8** (89:11 er) and cleared the way for the assembly of the polyene side chain and the known methyl phosphonate **11**.[4]

Initial experiments on the olefination of protected aldehyde **8** (1.8 equiv) with phosphonate **11** (1.0 equiv) under our modified Horner–Wadsworth–Emmons[13] (HWE) conditions (LiOH 2.0 equiv, THF–H_2O, 4:1, 1.5 d) gave low yields (<30%) accompanied by formation of β-keto phosphonate analogues to **13**, supposedly through a Knoevenagel-type process.[14] We therefore decided to screen other reaction conditions, which would also give us insight into the role of different additives and hopefully increase yield. The results of this qualitative ultra performance liquid chromatography–mass spectrometry (UPLC-MS) screening on the test substrate **10** are summarized in Table 1.

Comparing the product formation under the conditions in Table 1 entries 1 and 2 revealed that upon addition of water in presence of DBU the product distribution did not change considerably, as both products were observed. Under Masamune–Roush conditions[15] (entry 3), the formation of the Knoevenagel product **13** was not observed, and a solvent mixture of tetrahydrofuran–water (4:1) in the presence of lithium chloride accelerated formation of the HWE product **12** (entry 4), which might be attributed to a solubility effect. Screening conditions in entries 5 and 6 further attested to these observations, as using lithium hydroxide as a base and internal Li^+ source in the presence of water led to almost quantitative product formation while preventing side product formation. It should also be noted that under the conditions in entry 1, the Knoevenagel product **13** was not observed 24 hours after addition of lithium hydroxide (1 equiv) and a few drops of water, suggesting it might be hydrolyzed under basic aqueous conditions.

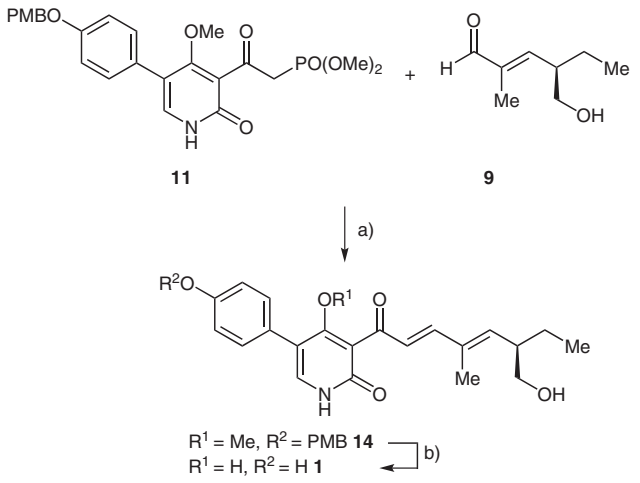
Table 1 Optimization of the Conditions of the HWE Reaction Using UPLC-MS Screening



Entry	Conditions[a]	Conversion (%) HWE product **12**	Knoevenagel product **13**
1	DBU (1.2 equiv), THF	<50	<50
2	DBU (1.2 equiv), THF–H_2O (4:1)	<50	<50
3	DBU (1.2 equiv), LiCl (2 equiv), THF	<50	–[b]
4	DBU (1.2 equiv), LiCl (2 equiv), THF–H_2O (4:1)	>50	–[b]
5	LiOH (1.2 equiv), THF	<50	traces
6	LiOH (1.2 equiv), THF–H_2O (4:1)	>50	–[b]

[a] Conditions: **10** (1 equiv), **11** (1 equiv), r.t. under exclusion of light.
[b] Not observed.

Taking into account these findings, we then chose to opt for the free alcohol **9**, obtained by deprotection of **8** (TBAF 1 equiv, r.t., 2 h, 95%). UPLC-MS monitoring of the subsequent HWE reaction revealed that a prolonged reaction time (6 d) was necessary to give the three-fold substituted pyridone **14** in 77% yield as the all-*E* isomer after flash chromatography (Scheme 2). Surprisingly, NMR analysis of the crude reaction after workup did not indicate the presence of the *Z*-isomer. According to our experience, these HWE reactions usually tend to give inseparable *E*/*Z* mixtures even under optimized conditions.



Scheme 2 *Reagents and conditions*: (a) **9** (1.2 equiv), LiOH (2.0 equiv), THF–H_2O (4:1), light exclusion, r.t., 6 d, 77%, *E*/*Z* >30:1; (b) 1. LiI (4 equiv), Py·HCl (6.0 equiv), 71%; ii. TFA (5% in CH_2Cl_2), 83%, *E*/*Z* >30:1, 93:7 er.

With the coupling product **14** in hand, the total synthesis was completed by an established[4,7] two-step deprotection sequence. The 4-methoxy group was cleaved in the presence of lithium iodide hydrate (4.0 equiv) and pyridine hydrochloride (6.0 equiv) under microwave heating (60 °C) in tetrahydrofuran in 71% yield. The obtained crude *E*/*Z* mixture (>5:1) was then stirred in trifluoroacetic acid (5% v/v in CH_2Cl_2) for 30 minutes, which gave after purification fully deprotected pyridovericin (**1**) in 83% yield (*E*/*Z* >6:1). A cascade of fractionated crystallizations from dichloromethane–methanol and pentane gave an analytical sample of pyridovericin with *E*/*Z* >30:1 and 93:7 er ratios determined by HPLC analysis, supporting that no racemization occurred in our reaction sequence. The analytical data of the synthetic material were found to be identical in all respects in comparison with the published values,[5] and the previously assigned[6c] *R*-configuration of naturally occurring pyridovericin (**1**) was corroborated by the measured optical rotation.

Conclusion

In summary, we have achieved the enantioselective total synthesis of the natural *R*-enantiomer of pyridovericin (**1**) with 93:7 er that did not erode during the synthesis. UPLC-MS screening also revealed that basic aqueous conditions in the presence of Li^+ were the optimal conditions for the second key step, the HWE reaction merging the two building blocks. Under these conditions, product formation was considerably accelerated and no Knoevenagel product **13** was observed. After two deprotection steps, synthetic pyridovericin was obtained that could be purified by fractionated crystallization. We are currently trying to expand our knowledge of the reported biological activity of pyridovericin[8] and pyridone alkaloids in general.

Reactions involving air or moisture sensitive reagents or intermediates were performed under an argon atmosphere in flame-dried glassware. Concentration under reduced pressure was performed by rotary evaporation at 40 °C, unless specified otherwise. Yields refer to purified, dried, and spectroscopically pure compounds. Reagents were purchased from Sigma-Aldrich and used without further purification unless stated otherwise. Technical grade solvents were distilled before use for workup and chromatography. Solvents used for chemical transformations were either puriss. quality or dried by filtration through activated alumina under argon or N_2 (H_2O content <10 ppm, Karl–Fischer titration) in a PureSolve MD 5 solvent purification system and then stored under argon over activated molecular sieves. TLC was performed on Merck silica gel 60 F254 plates (0.25-mm thickness) precoated with fluorescent indicator. The developed plates were examined under UV light and stained with $KMnO_4$ followed by heating. Flash chromatography was performed using silica gel 60 (230–240 mesh) from Fluka at 0.3–0.5 bar pressure. Reactions under microwave irradiation were performed in a Biotage Initiator$^+$ microwave synthesizer. ^1H and ^{13}C NMR spectra were recorded either using Bruker Avance 400 MHz, Bruker Avance DRX 500 MHz, or Bruker DRX 600 MHz spectrometers at r.t.; spectra were calibrated relative to the solvent residual proton chemical shift and the solvent residual carbon chemical shift.[16] Optical rotations $[\alpha]_D$ were measured at the Na D line (1-mL cell, 1-dm path length, Jasco P-2000 digital polarimeter, 25 °C); concentration *c* in g/100 mL in the indicated solvent. IR spectra were recorded using a Varian 800 FT-IR ATR spectrophotometer. HRMS-ESI data was recorded by the Mass spectrometric Service of the University of Bern on a Sciex QSTAR Pulsar mass spectrometer using electrospray ionization. UPLC-MS analysis was performed on an Agilent 1290 Infinity LC system with an Eclipse plus C18 (1.8 μm, 50 × 2.1 mm) column and an Agilent Technologies 6130 Quadrupol mass spectrometer using ESI-API. The solvents used were MeCN–0.1% TFA (solvent A) and H_2O–1% MeCN–0.1% TFA (solvent B); gradient: 0.0–0.4 min 95% B; 0.4–3.0 min 95% B to 95% A; 3.0–4.0 min 95% A at a flow rate of 1 mL/min. Semi-preparative RP-HPLC was performed on a Thermo Scientific Ultimate 3000 system using a Phenomenex Gemini 10μ C18 110A (150 × 10.0 mm) column eluting with gradients of MeCN in H_2O at a flow rate of 5 mL/min. Enantiomeric ratios (er) were determined by chiral HPLC on a Shimadzu Class-VP Version 5.0 system with a SCL-10A system controller, LC-10AD pump system, SIL-10AD auto injector, CTO-10AC column oven, DGU-14A degasser and SPD-M10A diode array- or UV/VIS detector at 20 °C with the stated solvent gradients and columns.

Methyl (*S*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]butanoate (6)

A high pressure steel autoclave (Premex Reactor AG; Lengnau, Switzerland; Model HPM-005) with a dry glass insert and a magnetic stirrer bar was charged with methyl (*E*)-2-[(*tert*-butyldimethylsiloxy)methyl]but-2-enoate (**5**, 184 mg, 500 μmol, 1.0 equiv) and anhyd CH_2Cl_2 (2.5 mL) and then the catalyst [Ir(L)(cod)]{B[3,5-$(CF_3)_2C_6H_3]_4$} (1 mol%) was added. The autoclave was closed and attached to a high-pressure hydrogen line and purged with H_2. The autoclave was sealed under 50 bar of H_2 pressure and the mixture was stirred at 900 rpm for 16 h at r.t. The H_2 was released, the solu-

tion was concentrated in a stream of N_2, diluted with hexane–MTBE (4:1, 1 mL), and passed through a short plug of silica gel in a Pasteur pipette, and the filtrate was concentrated in a stream of N_2 to give the pure **6** (184 mg, 500 μmol, quant.; 93:7 er). Analytical data are in full agreement with previously reported values,[7] except for inverted optical rotation of $[\alpha]_D^{25}$ +102 (*c* 0.89, $CHCl_3$);

93:7 er [HPLC (Chiralcel OD-H column, hexane–*i*-PrOH, 99:1, flow rate 0.5 mL/min, UV 230 nm): t_R = 8.11 (minor), 9.10 min (major)].

(*S*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]butanal

To a –78 °C cold solution of ester **6** (370 mg, 1.04 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (4 mL) was added 1 M DIBAL-H in CH_2Cl_2 (1.15 mL, 1.15 mmol, 1.1 equiv) portionwise (100 μL every 5 min); the solution was precooled by allowing it to run down the wall of the flask. This mixture was then stirred at –78 °C for 1 h and then quenched by slow addition of a mixture of MeOH–CH_2Cl_2 (1:1, 2 mL); the solution was precooled by running down the wall of the flask. The mixture was diluted with Et_2O (20 mL) and then quickly poured into sat. aq sodium potassium tartrate soln (20 mL). The resulting gray slurry was stirred vigorously until two clear layers were observed (~1 h), and these were then separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and the solvents removed in vacuo. Flash chromatography (pentane–Et_2O, 15:1) gave the title aldehyde (289 mg, 849 μmol, 82%) as a colorless oil. Analytical data are in full agreement with previously reported values,[7] except for the inverted optical rotation of $[\alpha]_D^{25}$ +16.7 (*c* 0.83, $CHCl_3$).

Ethyl (*R*,*E*)-4-[(*tert*-Butyldiphenylsiloxy)methyl]-2-methylhex-2-enoate (7)

To a solution of (*S*)-2-[(*tert*-butyldiphenylsiloxy)methyl]butanal (257 mg, 753 μmol, 1.0 equiv) in anhyd CH_2Cl_2 (3 mL) was added ethyl 2-(triphenylphosphoranylidene)propanoate (409 mg, 1.13 mmol, 1.5 equiv) in one portion. The resulting yellow solution was heated to reflux and the consumption of the aldehyde was followed by ^{1}H NMR; after 24 h a further portion of the phosphorane (136 mg, 376 μmol, 0.5 equiv) was added. After complete consumption of the aldehyde (48 h), the solvent was removed in vacuo and the crude slurry was directly subjected to flash chromatography (pentane–Et_2O, 25:1) to afford ester **7** (304 mg, 715 μmol, 95%; *E*/*Z* >30:1; 91:9 er) as a colorless oil; R_f = 0.33 (pentane–Et_2O, 15:1); $[\alpha]_D^{25}$ +6.27 (*c* 0.93, $CHCl_3$); 91:9 er [HPLC (Chiralpak IC column, hexane–*i*-PrOH, 99:1, flow rate 0.5 mL/min, UV 206 nm): t_R = 11.1 (minor), 11.5 min (major)].

FT-IR (neat): 2962, 2933, 2859, 1710, 1463, 1388, 1229, 1107, 741, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 4 H, CH_{Ar}), 7.45–7.35 (m, 6 H), 6.59 (dq, *J* = 10.3, 1.3 Hz, 1 H), 4.28–4.14 (m, 2 H), 3.63–3.53 (m, 2 H), 2.60–2.50 (m, 1 H), 1.81 (d, *J* = 1.4 Hz, 3 H), 1.72–1.63 (m, 1 H), 1.35–1.25 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.03 (s, 9 H), 0.84 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.4, 143.9, 135.8, 133.8, 129.8, 129.2, 127.8, 66.4, 60.6, 43.5, 26.9, 24.2, 19.4, 14.5, 13.1, 11.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{36}O_3NaSi$: 447.2326; found: 447.2319.

(*R*,*E*)-4-[(*tert*-Butyldiphenylsiloxy)methyl]-2-methylhex-2-en-1-ol

To a –78 °C cold solution of ester **7** (300 mg, 706 μmol, 1.0 equiv) in anhyd THF (3 mL) was added dropwise 1 M DIBAL-H in hexane (2.12 mL, 2.12 mmol, 3 equiv). The solution was stirred for 20 min at –78 °C, 30 min at 0 °C, and finally 1 h at r.t., after which TLC indicated complete consumption of the starting material. The reaction was quenched by dropwise addition of MeOH (2 mL), diluted with Et_2O (20 mL), and then quickly poured onto sat. aq sodium potassium tartrate soln (20 mL). The resulting gray slurry was stirred vigorously until two clear layers were observed (~2 h), and these were then separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and the solvents removed in vacuo. Flash chromatography (pentane–Et_2O 4:1) gave the title alcohol (249 mg, 621 μmol, 88%; *E*/*Z* >30:1; 89:11 er) as a colorless oil; R_f = 0.30 (pentane–Et_2O 4:1); $[\alpha]_D^{25}$ –24.6 (*c* 1.1, $CHCl_3$); 89:11 er [HPLC (Chiralcel AD-H column, hexane–*i*-PrOH, 99:1, flow rate 0.6 mL/min, UV 206 nm): t_R = 15.3 (major), 17.3 (minor)].

FT-IR (neat): 3324 (br), 2958, 2930, 2857, 1389, 1427, 1111, 1007, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.45–7.35 (m, 6 H), 5.13 (dq, *J* = 9.8, 1.1 Hz, 1 H), 3.98 (d, *J* = 5.9 Hz, 2 H), 3.60–3.50 (m, 2 H), 2.48–2.37 (m, 1 H), 1.71–1.58 (m, 1 H), 1.62 (d, *J* = 1.1 Hz, 3 H), 1.27–1.15 (m, 2 H), 1.05 (s, 9 H), 0.84 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.4, 135.8, 134.2, 129.7, 128.0, 127.7, 69.1, 67.2, 42.3, 27.0, 24.7, 19.4, 14.3, 11.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{35}O_2Si$: 383.2401; found: 383.2401.

(*R*,*E*)-4-(Hydroxymethyl)-2-methylhex-2-enal (9)

To a solution of (*R*,*E*)-4-[(*tert*-butyldiphenylsiloxy)methyl]-2-methylhex-2-en-1-ol (160 mg, 397 μmol, 1.0 equiv) in anhyd CH_2Cl_2 (3 mL) was added powdered molecular sieves (50 mg, 4 Å, stored at 120 °C) and NMO (70.0 mg, 596 μmol, 1.5 equiv). To this slurry, TPAP (3.5 mg, 10.0 μmol, 0.025 equiv) was added and the resulting black suspension was stirred for 1 h at r.t.; TLC indicated complete consumption of the starting material. The crude mixture was filtered over a plug of silica, which was further washed with CH_2Cl_2 (70 mL). The solvents were removed in vacuo to give the protected aldehyde **8** as a yellow oil (155 mg, 397 μmol, 99%), which was used without further purification in the next step; R_f = 0.45 (pentane–Et_2O, 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 7.64–7.60 (m, 4 H), 7.46–7.35 (m, 6 H), 6.27 (dq, *J* = 10.2, 1.3 Hz, 1 H), 3.70 (dd, *J* = 10.0, 5.3 Hz, 1 H), 3.62 (dd, *J* = 10.0, 6.6 Hz, 1 H), 2.73 (dddt, *J* = 10.2, 9.0, 6.4, 5.2 Hz, 1 H), 1.72 (d, *J* = 1.3 Hz, 3 H), 1.71–1.62 (m, 1 H), 1.41–1.31 (m, 1 H), 1.03 (s, 9 H), 0.84 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 195.5, 156.7, 135.6, 135.5, 129.8, 127.7, 66.1, 43.7, 26.8, 24.0, 11.7, 9.7.

To a solution of the crude aldehyde **8** (179 mg, 447 μmol 1.0 equiv) in anhyd THF (3 mL) was added 1 M TBAF in THF (450 μL, 450 μmol 1.0 equiv) and the resulting dark yellow solution was stirred at r.t.; after 2 h, UPLC-MS indicated complete consumption of the starting material. The mixture was poured into sat. aq NH_4Cl (10 mL) and extracted with Et_2O (5 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvents removed in vacuo. Flash chromatography (pentane–Et_2O, 1:10) gave the deprotected aldehyde **9** (60.3 mg, 424 μmol, 95%, *E*/*Z* >30:1) as a colorless oil; $[\alpha]_D^{25}$ –26.6 (*c* 0.90, $CHCl_3$); R_f = 0.45 (pentane–Et_2O, 1:10).

FT-IR (neat): 3363 (br), 2962, 2931, 2876, 2361, 2335, 1685, 1042, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1 H), 6.32 (dq, *J* = 10.1, 1.3 Hz, 1 H), 3.75–3.60 (m, 2 H), 2.84–2.71 (m, 1 H), 1.80 (d, *J* = 1.4 Hz, 3 H), 1.72–1.62 (m, 1 H), 1.46–1.34 (m, 1 H), 0.91 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.3, 155.5, 141.4, 65.6, 43.9, 24.1, 11.8, 10.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{15}O_2$: 143.1067; found: 143.1066.

3-[(*R*,2*E*,4*E*)-6-(Hydroxymethyl)-4-methylocta-2,4-dienoyl]-4-methoxy-5-[4-(4-methoxybenzyloxy)phenyl]pyridin-2(1*H*)-one (14)

To a suspension of the aldehyde **9** (36.0 mg, 253 μmol, 1.2 equiv) and the phosphonate **11**[4] (103 mg, 211 μmol, 1.0 equiv) in THF–H_2O (4:1, 1 mL) was added $LiOH·H_2O$ (17.7 mg, 422 μmol, 2.0 equiv). A yellow solution formed immediately, which was stirred under exclusion of light at r.t. and monitored by UPLC-MS. After 6 d, the dark orange mixture was poured into sat. aq NH_4Cl (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvents removed in vacuo. Flash chromatography (CH_2Cl_2–MeOH, 20:1) gave the pyridopolyene **14** (82.0 mg, 162 μmol, 77%, *E*/*Z* >30:1) as a yellow oil; R_f = 0.30 (CH_2Cl_2–MeOH, 20:1).

FT-IR (neat): 3400 (br), 2934, 2358, 1634, 1611, 1512, 1237, 1033, 830, 733 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 12.91 (br s, 1 H), 7.40–7.35 (m, 3 H), 7.32–7.27 (m, 2 H), 7.22 (d, *J* = 15.8 Hz, 1 H), 7.01–6.97 (m, 2 H), 6.95–6.91 (m, 2 H), 6.50 (d, *J* = 15.8 Hz, 1 H), 5.74 (d, *J* = 10.1 Hz, 1 H), 5.01 (s, 2 H), 3.82 (s, 3 H), 3.64–3.59 (m, 1 H), 3.61 (s, 3 H), 3.52–3.46 (m, 1 H), 2.68–2.58 (m, 1 H), 1.89 (d, *J* = 1.0 Hz, 3 H), 1.59–1.52 (m, 1 H), 1.32–1.22 (m, 1 H), 0.86 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 194.2, 168.4, 165.6, 164.4, 159.7, 158.7, 150.6, 145.4, 145.2, 136.0, 135.2, 130.0, 129.4, 129.3, 126.9, 126.4, 114.8, 113.9, 69.8, 68.8, 60.7, 55.2, 43.9, 24.2, 13.0, 11.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{34}O_6N$: 504.2381; found: 504.2377.

(–)-Pyridovericin (1)

A suspension of the pyridopolyene **14** (74 mg, 147 μmol, 1.0 equiv), $LiI·3H_2O$ (111 mg, 589 μmol mol, 4.0 equiv) and pyridine hydrochloride (102 mg, 883 μmol, 6.0 equiv) in degassed (freeze/thaw) THF (4 mL) was heated to 60 °C for 4 h in a microwave reactor. The yellow suspension was poured into brine (5 mL) and then extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvents removed in vacuo. Flash chromatography (CH_2Cl_2–MeOH, 20:1) gave the crude demethylated pyridone (51 mg, 104 μmol, 71%, *E*/*Z* >5:1) as a yellow oil. ^1H NMR data is given for the *E* isomer; R_f = 0.40 (CH_2Cl_2–MeOH, 15:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 11.59 (s, 1 H), 7.98 (d, *J* = 15.4 Hz, 1 H), 7.62 (d, *J* = 15.4 Hz, 1 H), 7.44–7.33 (m, 5 H), 7.07–6.98 (m, 2 H), 6.98–6.89 (m, 2 H), 5.82 (d, *J* = 10.0 Hz, 1 H), 5.01 (s, 2 H), 3.82 (s, 3 H), 3.71–3.60 (m, 1 H), 3.56–3.45 (m, 1 H), 2.75–2.60 (m, 1 H), 1.94 (s, 3 H), 1.63–1.53 (m, 1 H), 1.34–1.24 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

The crude pyridone (16 mg, 33 μmol, 1.0 equiv) was suspended in CH_2Cl_2 (2 mL) and TFA (100 μL, 5% v/v final concentration) was added dropwise. The formed yellow solution was stirred at r.t. for 30 min, after which TLC indicated complete consumption of the starting material. The crude solution was poured into sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2–MeOH–EtOAc (6:1:1, 5 × 10 mL), after which the aqueous layer appeared to be colorless. The combined yellow organic layers were dried (Na_2SO_4), filtered, and the solvents removed in vacuo. Flash chromatography (CH_2Cl_2–MeOH, 20:1) gave (–)-pyridovericin (**1**) (10 mg, 27 μmol, 83%, *E*/*Z* >6:1) as a yellow oil. Fractional crystallization was achieved by dissolving the crude material in MeOH–CH_2Cl_2 (1:9, 300 μL) and dropwise addition of pentane (1.2 mL) while swirling vigorously. The yellow suspension was stored at 5 °C for 10 min, centrifuged and the supernatant removed carefully with a syringe. After 5 repetitions of the process, this gave an analytical sample of **1** (3 mg) as an amorphous yellow solid; *E*/*Z* >30:1; 93:7 er; R_f = 0.17 (CH_2Cl_2–MeOH, 15:1); $[\alpha]_D^{25}$ –10.8 (*c* 0.16, MeOH); 93:7 er [HPLC (Chiralcel IC column, hexane–*i*-PrOH, 70:30, flow rate 1.0 mL/min, UV 206 nm): t_R = 8.3 (minor), 9.2 min (major)].

FT-IR (neat): 3287 (br), 2960, 2929, 2360, 2341, 1648, 1610, 1518, 1460, 1263, 1215, 1037, 985, 835, 769 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 17.56 (s, 1 H), 11.62 (s, 1 H), 9.48 (s, 1 H), 7.99 (d, *J* = 14.9 Hz, 1 H), 7.55 (s, 1 H), 7.51 (d, *J* = 15.6 Hz, 1 H), 7.30–7.24 (m, 2 H), 6.81–6.75 (m, 2 H), 5.94 (d, *J* = 9.6 Hz, 1 H), 4.59 (t, *J* = 5.4 Hz, 1 H), 3.41–3.30 (m, 2 H), 2.57–2.49 (m, 1 H), 1.85 (s, 3 H), 1.65–1.54 (m, 1 H), 1.28–1.17 (m, 1 H), 0.82 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 193.7, 176.9, 161.8, 156.7, 149.4, 147.5, 140.7, 134.5, 130.1, 123.5, 123.1, 115.0, 112.8, 106.0, 64.0, 43.6, 24.0, 12.8, 11.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{24}O_5N$: 370.1649; found: 370.1647.

UV: λ_{max} (MeCN–H_2O, 60:40) = 206, 249, 338 nm.

Dimethyl {(2*Z*,4*E*,6*E*)-1-[4-Methoxy-5-[4-(4-methoxybenzyloxy)phenyl]-2-oxo-1,2-dihydropyridin-3-yl]-6,8-dimethyl-1-oxodeca-2,4,6-trien-2-yl}phosphonate (13)

The phosphonate **11**[4] (9.5 mg, 20 μmol, 1.0 equiv) and aldehyde 10 (5.7 mg, 19.5 μmol, 1.0 equiv) were suspended in anhyd THF (0.3 mL) and 1 drop of DBU was added. The suspension was stirred for 24 h at r.t. under exclusion of light, poured into sat. aq NH_4Cl (2 mL), extracted with CH_2Cl_2 (5 × 3 mL), dried (Na_2SO_4), filtered, and evaporated. The crude yellow oil was purified by flash chromatography (CH_2Cl_2–MeOH, 20:1) to give the HWE product (4.0 mg, 7.8 μmol, 40%) and the crude Knoevenagel product. This was further purified by semipreparative HPLC (95% MeCN to 100% H_2O in 25 min) to give the desired Knoevenagel product (4.0 mg, 6.4 μmol, 30%) as a mixture of 4 *E*/*Z* isomers. NMR data is given for the major all-*E* isomer. Most ^1H shifts were assigned from 2D-NMR spectra (see the Supporting Information). The signal of the carbon atom at the C3 position of the pyridone could not be detected.

R_f = 0.15 (CH_2Cl_2–MeOH 20:1).

FT-IR (neat): 2957, 2853, 2361, 1589, 1643, 1513, 1462, 1387, 1292, 1243, 1177, 1030, 791, 649 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 12.62 (br s, 1 H), 7.62 (dd, *J* = 14.7, 11.6 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.9 Hz, 2 H), 7.27 (s, 1 H), 7.27 (dd, *J* = 33.0,11.6 Hz, 1 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 6.77 (d, *J* = 14.7 Hz, 1 H), 6.39 (d, *J* = 8.5 Hz, 2 H), 5.67 (d, *J* = 9.7 Hz, 1 H), 5.01 (s, 2 H), 3.83 (d. *J* = 2.8 Hz, 6 H), 3.74 (s, 3 H), 3.58 (s, 3 H), 2.50–2.39 (m, 1 H), 1.87 (s, 3 H), 1.44–1.35 (m, 1 H), 1.33–1.22 (m, 1 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 0.82 (t, *J* = 7.40 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 193.0, 168.2, 165.0, 163.6, 162.2, 160.7, 159.5, 158.5, 154.8, 149.7, 134.9, 133.7, 130.0, 129.2, 128.9, 123.2, 117.0, 114.9, 114.0, 69.8, 60.4, 54.3, 52.8, 35.0, 29.8, 20.1, 12.7, 11.9.

^{31}P NMR (243 MHz, $CDCl_3$): δ = 17.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{41}O_8NP$: 622.2564; found: 622.2565.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^1H and ^{13}C NMR spectra and HPLC traces.

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